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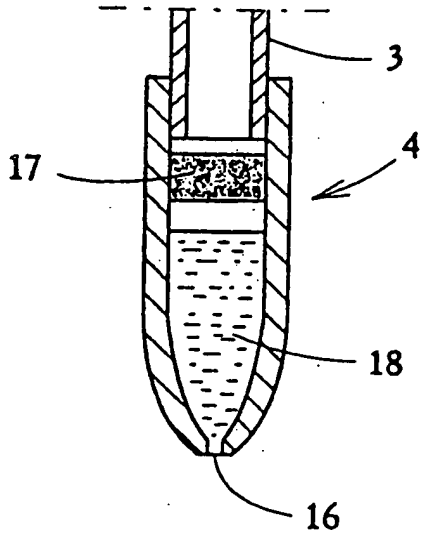
(54) Title: A METHOD AND AN EQUIPMENT FOR PORTIONING LIQUID CONSIGNMENTS

(57) Abstract

This invention relates to a method and an equipment for portioning of liquid consignments of specific amounts and to the packaging of these small liquid consignments in mass production. The portioning is executed with a bellow, which lines an air space of varying volume so that the air stream caused by the bellow establishes the injection and suction of a liquid. According to the invention the air space is connected to the suction tip (4), which holds a liquid space lined by a filter permeable to air stream but impermeable to liquid; when in suction phase the liquid is sucked into the suction tip (4) by the motion of the liquid, and in the injection phase the reverse motion of the bellow is used in injecting the liquid consignment from the suction tip, and the injection of the liquid consignment of certain volume is based on a corresponding volume change in the air space of the bellow established by an equipment controlling the bellow. Serial portioning may take place so that a liquid volume of multiple times of the liquid consignments is sucked into the suction tip (4), after which the liquid consignments are portioned by the reversible motions of the bellow produced by the equipment controlling the bellow, which may be a pacemotor, for example. The suction tip may be removable, in which case the liquid to be portioned may be changed without having to clean the equipment, since the filter (17) in the suction tip prevents the contamination of the air space of the bellow.



A method and an equipment for portioning liquid consignments

This invention relates to a method and an equipment for portioning liquid consignments of specific amounts. In addition, the invention comprises the use of the equipment in packaging of small liquid consignments.

Liquids which are sold in small consignments, such as pharmaceutical products and reagents, have been packed in tubes, bottles, or other similar containers with an equipment, which automatically fills and closes the container and attaches an etiquette to it. On the packaging lines concerned the liquid to be packed is typically led through a portioner or a part of the portioner, while the portioning space is full of the liquid concerned. Peristaltic pumps and rotating piston pumps, among others, have been used as portioners with liquid consignments of the magnitude of few milliliters.

The patent document US 4,987,726 features a certain packaging line of pharmaceutical liquids in accordance with the prior art, where the liquid, driven by the hydrostatic pressure, flows from an upper container to bottles which are preceding on the packaging line.

The above described technique is severely inadequate in the respect that, if the equipment is used in packaging several products, then due to the risk of contamination the portioning spaces and tubes have to be emptied and cleaned thoroughly every time a change is made from one product to the next. These difficult and time consuming manouvers present a serous impediment especially when the consignments are small, typically in the range of 100-5000 packages, and the product repertuare is diverse.

The objective of the invention is to establish a solution, which removes the disadvantages associated with cleaning problems in accordance with the prior art, and makes it possible to switch quick from packaging or portioning one liquid to packaging or portioning the next liquid. The method in accordance with the invention is characterised by the portioning being executed with a bellow, which establishes the suction and the injection of the liquid with an air stream, and the air space lined out by the bellow is in conjunction with a suction tip, which contains a liquid space limited by a filter permeable to the air stream but impermeable to the liquid, and when in suction phase the movement of the bellow is being used in sucking the liquid to the suction tip, and when in the injection phase an opposite

movement of the bellow is being used in injecting the liquid consignment to be portioned from the suction tip, and the injection is being based on a change in volume of the air space of the bellow, corresponding to the volume of the liquid consignment, established by an equipment controlling the bellow.

The relevant advantage of the invention in comparison to the prior art is that, the liquid to be portioned is taken only in the suction tip, from which during portioning it is injected by a change of direction in the air stream. The suction tip may be a simple tube equipped with a filter, where the filter prevents the liquid from entering the bellow, while allowing the air stream of the bellow to pass through at the same time for establishing the suction and injection of the liquid. By this the contamination of the bellow acting as a portioner is prevented, and the need for cleaning the bellow ceases to exist.

With regards to the the equipment controlling the bellow, a reference is made to a former application FI 94675 of the applicant. In this document, which relates to the accurate portioning of small liquid batches, and where the bellow acts as a liquid filled portioning space, the establishment of small volume changes with a calibrated equipment such as a pacemotor, pietzorod or servomotor has been described in detail. In the case of the invention concerned any special calibration is usually unnecessary, because while the bellow functions with air instead of liquid the accuracy of the portioning with liquid consignments of 1 milliliter or smaller is despite the calibration of the order of 1%. This is an adequate accuracy even in portioning of very expensive products, where an excess dose causes financial losses to the producer.

According to the invention the suction tip is preferably removable, and the filter it contains is a sterile aerosol filter, which is permeable to air stream but impermeable to liquid drops of any size. During portioning the liquid to be portioned can be changed simply by changing the suction tip, which may happen in a couple of seconds. Since the suction tips are disposable, changing from one liquid to another requires no cleaning procedures.

In mass production a volume multiples times of any consignment or portion may be sucked into the suction tip. For example 5-20-fold volume may be portioned to a series of packages by volume changes established by sequential movements of the bellow. After the portioning sequence is over, the same suction tip may be filled again with the same liquid or the product may be changed by changing the suction tip.

According to the invention, the suction tip may be kept clean by blowing air with the bellow through the suction tip immediately before the sucking of the liquid. In the intake of air of the bellow the suction tip comprising the filter is in place, and the filter prevents the contamination of the bellow. When the direction is reversed, the bellow begins to "flush" the suction tip clean air. The bellow and the suction tip are hereby free of contamination, if the the tip is immersed in the liquid container every time during suction, and the air is being blown the same way every time inbetween the emptying of the suction tip and a new refill.

Very suitable liquids for portioning into packages in accordance with the invention are especially enzyme products, which have a high price and very small package size, preferably below 1 ml. The preferable amount to be sucked into the suction tip may be, for example, between 500-2000 microliters, from which for example 5-500 microliters, preferably 20-100 microliters are portioned per package. A 1000 microliter suction tip may be used, which is sucked to its full volume, and from which the liquid is portioned into 20 liquid packages of 50 microliters, which is appropriate, for example, for portioning of restriction enzymes into Eppendorf tubes.

The equipment in accordance to the invention and in accordance to the method described above comprise a bellow, which facilitates injection and suction by its reversible movements. The equipment is characterised by the bellow lining out an air space, which is in conjunction with a suction tip, which has liquid space limited by a filter permeable to air stream but impermeable to liquid, and to this liquid space the liquid to be portioned may be sucked or injected, and that the bellow is in conjunction to the equipment controlling it, which establishes a volume change in the airspace of the bellow corresponding to the size of the liquid consignment.

The air space of the bellow, the volume of which changes the portioning is based on, is preferably on the inside of the bellow, even though it may be an external space surrounding the bellow as well. The air space may be in connection to the suction tip through an air hose, which is preferably removable.The suction tip may be a simple tube, equipped with a an aerosol filter impermeable to liquid, and it may be adjoinable to the said air hose by pushing the ends of these two pieces so that they overlap and are squeezed to attach to each other.

The equipment controlling the bellow is preferably a pacemotor, whiches rotatory motion is transformable to linear motion which changes the volume of the bellow, for example by a pullable string or a band. The string or the band may be joined to the end of the bellow directly or through a lever mechanism. The sequential steps of

the pacemotor, which produce a series of essentially uniform consignments from the liquid sucked into the suction tip, may be empirically determined. Instead of the pacemotor the equipment may be a pietzorod or a servomotor, which while connected to the end of the bellow produce the linear motion directly, without any transmission mechanism.

The invention further comprises the use of the above described equipment in packaging of small liquid consignments in mass production. This concerns especially enzyme products, which typically have a package size of 20-500 micro-liters.

The invention is explained in more detail with examples with reference to the following drawings, of which,

Figure 1 schematically represents a portioning equipment according to the invention, where the suction and the injection are established with a bellow, which is moved by a pacemotor with the help of a lever and a pullable band rotatable around the axle of the motor,

Figure 2 represents an equipment in accordance with the figure 1 in the beginning of the injection phase seen from the view II-II.

Figure 3 represents an equipment in accordance with figure 2, but at the end of the injection phase.

Figure 4 represents a cut view of the suction tip of the equipment of figures 1-3 in a larger scale, and

Figure 5 represents portioning of liquid into packages preceding on a production line with the suction tip in accordance with figure 4.

The portioning equipment in accordance with figures 1-3 comprises a flexible, reversibly movable bellow 1 made of rubber or metal, and an internal air space 2 which establishes the portioning by its volume changes. The air space 2 of the bellow is connected to the removable suction tip 4 via the air channel 3. The suction of the liquid from cuvet 5 or from some other source is established by stretching the bellow 1 so, that the volume of internal air space 2 grows. Correspondingly the injection happens during the compression of the bellow 1 so, that the internal air space 2 contracts.

The motion of bellow 1 is facilitated by the rotatory axle 7, which is used by the pacemotor 6. The bottom of the bellow 1 is, as according to the figure 1, rigidly attached to the support structure 8, which supports the pacemotor 6 and its axles 7 as well. The end of the axle 7 is supported to the support structure 8 by the ball bearing 9. A pullable band 10 is attached to the axle 7, and the pullable band 10 is arranged to wind around the axle as represented in figure 2. The end of the pullable band 10 is attached to the lever 12 mounted to the support structure 8 with the ball bearing 11, and the lever 12 is attached to the bellow 1 via the joint lever 15 attached to its ends 13 and 14. The end of the bellow 1 hereby follows the mainly vertical motion of the lever 12 and pullable band 10 established by the rotation of the axle 7. This motion establishes the volume change of the air space 2 of the bellow 1 and hereby facilitates the injection or suction of a corresponding liquid consignment via the suction tip 4. In figure 2 the bellow 1 is in the initiation point of the portioning sequence, where the air space 2 of the bellow 1 is streched to its maximum position, and the figure 3 describes the end point of the portioning sequence, where the air space is contracted to a minimum. The contraction may be based on the spring force of the bellow 1, but also an additional spring (not featured here) may be used to help the bellow to contract.

The suction tip 4 at the end of the suction channel 3 comprises according to figure 4 a narrowing tube, open from its tip 16, and the tube holds a firmly set aerosol filter so, that there is a liquid space 18 between the tip 16 and the filter 17, to which the liquid to be portioned may be sucked. The aerosol filter 17 is permeable to a suction air stream, but holds all solid or liquid material or drops, and thereby prevents the contamination of the air channel 3 and the air space 2 of the bellow 1 by the liquid.

Figure 5 schematically represents the packaging line 19, with which using the suction tip 4 of figure 4 different liquid consignments 20 are portioned into packaging containers 21. The containers 21 one at a time pass by the suction tip 4, which fills each container with a liquid injected from the space 18, and the injection is based on the contraction of the bellow 1, which results in a volume change in air space 2.

In figure 2 the lever 12 used by the pacemotor is in its top position, when the volume of the air space 2 of the bellow is a maximum. In this initial position of portioning the liquid space 18 of the suction tip 4 is filled by the liquid sucked from the cuvet 5. The portioning is then facilitated by the pacemotor 6, when the axle 7 of figure 2 rotates anti-clockwise, and when the pullable band 10 is released from the axle and lets the bellow contract along with its spring force, a liquid volume

corresponding to the contraction of the airspace 2 is injected from the suction tip 4. After the injection the pacemotor 6 stops and starts again, when the rotation of the axle 7 produces the next portion, where essentially the same liquid volume is injected from the suction tip 4. This is continued, until a situation in accordance with figure 3 is met, where the liquid sucked into the liquid space 18 of the suction tip 4 has essentially been finished. If the volume of the liquid space 18 is of the order of 1 ml, for example, it is adequate for twenty liquid consignments of 50 microliter each without a refill. In practice the suction tip is not completely emptied, but after a portioning sequence the liquid space 18 of the tip 4 still holds some left-over liquid, which is injected to the cuvet 5 before a new refill. The refill is carried out by pacing the pacemotor to the opposite direction as in the case of portioning, when the pullable band 10 stretches the bellow 1 and the expansion of the air space 2 sucks liquid from cuvet 5 to the suction tip, after which the portioning may continue. Alternatively it is possible to change the liquid to be portioned, in which case the suction tip 4 at the end of the air channel 3 is replaced by another. Because the aerosol -filter 17 of the suction tip 4 has protected the bellow 1 and the air channel 3 from contamination, they need not be cleaned when the liquid is changed.

The portioning accuracy of the equipment was tested with portion sets of ten consecutive samples in different temperatures. The liquid to be portioned was a 50% glycerol solution, and a suction tip of 1 ml was used in portioning, which had the suction rate of 600 microliters/second and injection rate of 500 microliters/-second. The bellow used was a 2 ml nickel bellow, which was connected with a lever to a pullable string of polymer material wound around the axle of the pace-motor (Tamagava, 400 step) with a transmission ration 5:1 (the ratio of the motion of the string and the motion of the end of the bellow). The portion size was of the order of 50 microliters and the delay between consecutive portions was 1 s. The temperature of the first portioning set was -13 degrees Celsius, and the portion sizes in microliters were 54.1, 54.1, 53.1, 53.3, 53.3, 53.2, 53.0, 52.9, and 52.9. The average portion size is hereby 53.7 microliters and the standard deviation 0.7 micro-liters.

The following table displays the results of the corresponding measurement sets in different temperatures.

Table

Temperature (°C)	Average portion size (µl)	STD (µl)
-13	53.7	0.7
-12	53.3	0.5
-11	53.4	0.6
-10	53.3	0.7
-8	53.2	0.5
-7	53.2	0.3
-4	52.9	0.4
-3	53.2	0.6
÷2	53.4	0,5

It is obvious to one skilled in the art, that the applications of the invention are not restricted to the examples represented, but may vary within the scope defined by the following patent claims. It is possible to construct a bellow so, that the air space of varying volume lined by it is on the outside of the bellow. The form of the lever moving the bellow may vary, and it may be coupled with pullable band or bands to the axle of the pacemotor so, that the motor moves the bellow to both directions, i.e. both compresses and stretches it, regardless of the spring force of the bellow. As a substitute to the pullable band winding around the axle, may an eccentric axle wound by the motor and coupled to the end of the bellow be used. Alternatively the pacemotor may be replaced by a servomotor or a pietzorod, which may be coupled to the end of the bellow without any transmission mechanisms.

Claims

1. A method for portioning liquid consignments (20) of specific amounts, **characterised** in that the portioning is being executed with a bellow (1), which establishes the suction and the injection of the liquid with an air stream, and the air space (2) lined out by the bellow is in conjunction with a suction tip (4), which contains a liquid space (18) limited by a filter (17) permeable to the air stream but impermeable to the liquid, and when in suction phase the movement of the bellow is being used in sucking the liquid to the suction tip, and when in the injection phase an opposite movement of the bellow is being used in injecting the liquid consignment to be portioned from the suction tip, and the injection is being based on a change in volume of the air space of the bellow, corresponding to the volume of the liquid consignment, established by an equipment (6) controlling the bellow.

2. A method in accordance with claim 1, **characterised** in that the suction tip (4) is removable and holds a filter (17), which is a sterile aerosol filter, which is permeable to air stream but holds liquid drops.

3. A method in accordance with claim 1 or 2, **characterised** in that a liquid volume multiple times the liquid consignments is sucked into the suction tip (4), and a series of liquid consignments is portioned afterwards with the reversible motions of the bellow (1) established by the equipment, such as a pacemotor, controlling the bellow.

4. A method in accordance with any of the preceding claims, **characterised** in that the suction tip (4) is cleaned by letting the bellow (1) blow air through it immediately before the suction of the liquid to the suction tip.

5. A method in accordance with any of the preceding claims, **characterised** in that the method is used in portioning different liquids by changing the removable suction tip (4) in between portionings.

6. A method in accordance with any of the preceding claims, **characterised** in that the method is used in portioning of a liquid, such as an enzyme product, into packages (21).

7. A method in accordance with the claim 6, **characterised** in that the liquid volume sucked into the suction tip is approximately 500-2000 microliters.

8. A method in accordance with claim 6 or 7, **characterised** in that the liquid consignment (20) to be portioned per package (21) is of the order of 5-500 micro-liters, preferably approximately 20-100 microliters.

9. An equipment for a method for portioning liquid consignments (20) of specific amounts, in which the equipment comprises a bellow, which facilitates injection and suction by its reversible movements, **characterised** in that the bellow lines out an air space, which is in conjunction with a suction tip, which has liquid space limited by a filter permeable to air stream but impermeable to liquid, and to this liquid space the liquid to be portioned may be sucked or injected, and that the bellow is in conjunction to the equipment controlling it, which establishes a volume change in the airspace of the bellow corresponding to the size of the liquid consignment.

10. An equipment in accordance with the claim 9, **characterised** in that the suction tip (4) is removable and it comprises a filter (17), which is a sterile aerosol filter, which is permeable to air stream but impermeable to liquid drops.

11. An equipment in accordance with the claim 10, **characterised** in that the interior (2) of the bellow (1) is connected to the removable suction tip (4) via the air channel (3).

12. An equipment in accordance with any of the claims 9-11, **characterised** in that the equipment controlling the bellow (1) is a pacemotor (6), and the rotatory motion of the axle (7) used by the pacemotor is converted to the linear motion of the bellow (1).

13. An equipment in accordance with the claim 12, **characterised** in that the agent converting the motion is a pullable string or band woundable around the axle (7) of the motor (6).

14. The use of an equipment in accordance with the claims 9-13 in portioning of small liquid consignments (20) into packages (21) in mass production.

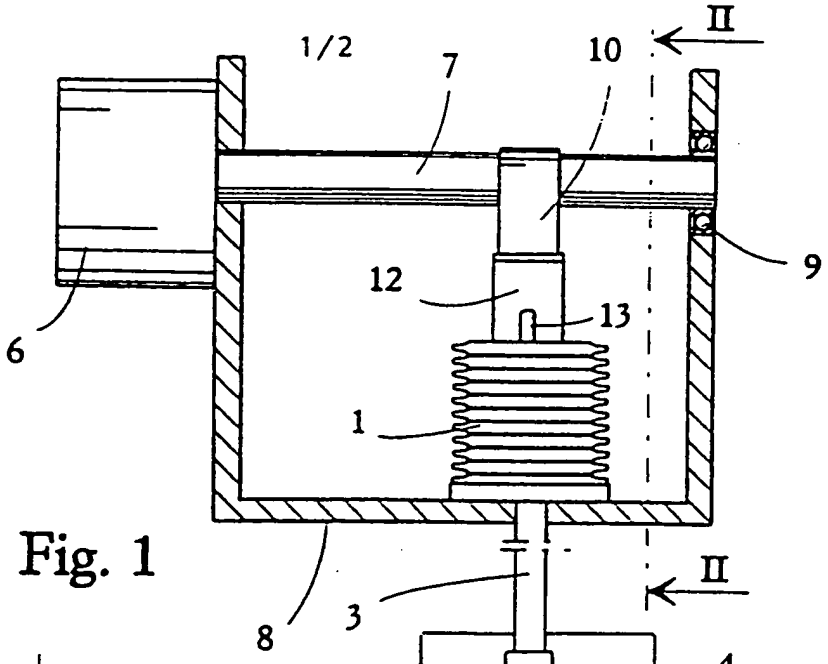


Fig. 1

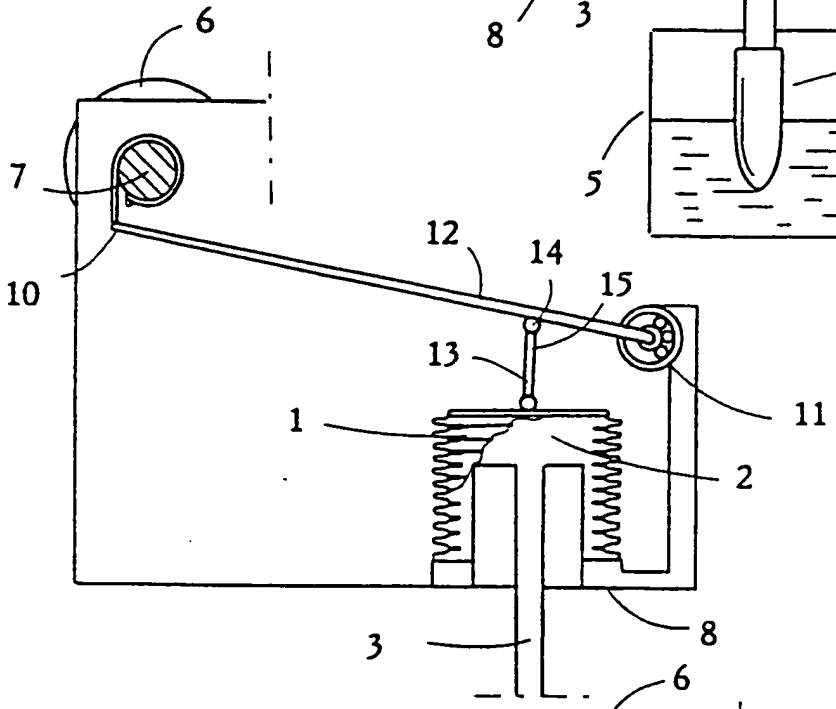


Fig. 2

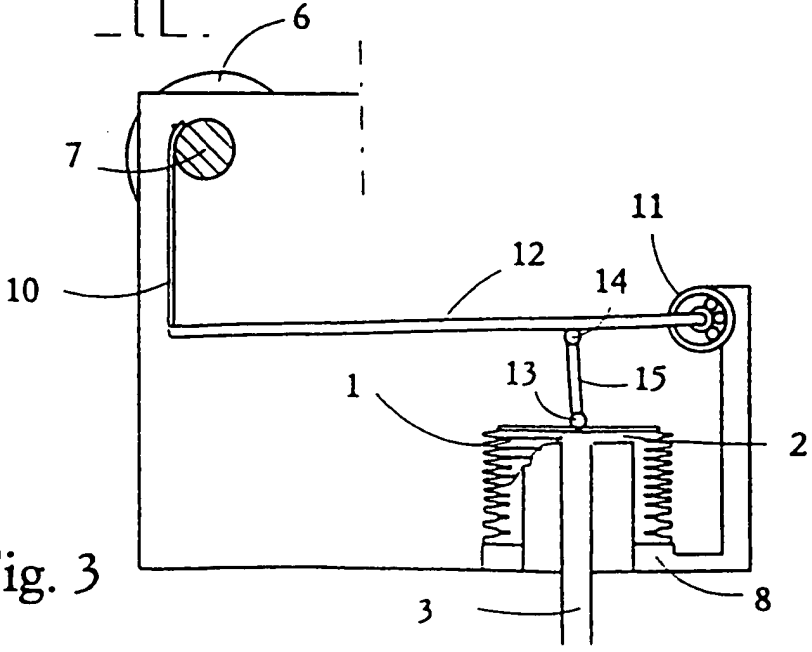


Fig. 3

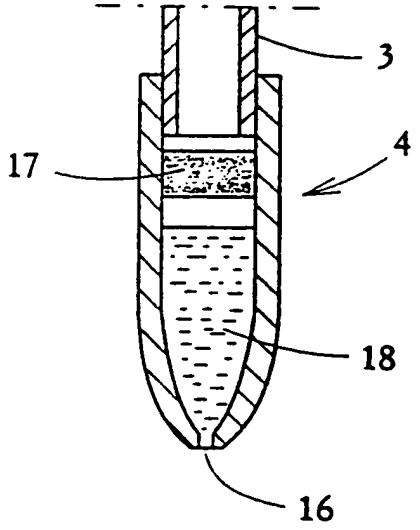


Fig. 4

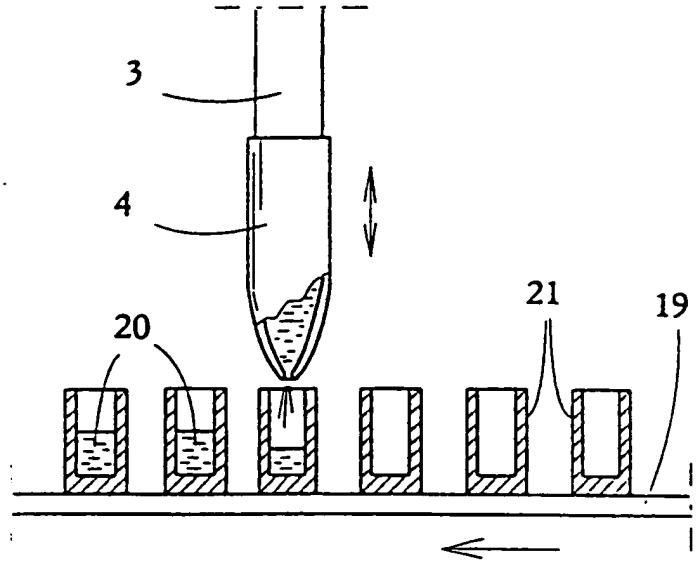


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 97/00603

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: G01F 11/00, B65B 3/30, B01L 3/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: B01L, B65B, G01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5364495 A (M.W. SMITH), 15 November 1994 (15.11.94), column 2, line 20 - line 56; column 6, line 52 - line 66	1,2,9-11
Y		1-14
	--	
X	US 5156811 A (D.A. WHITE), 20 October 1992 (20.10.92), column 1, line 16 - line 47; column 4, line 38 - column 5, line 2	1,2,4,9-11
	--	
X	US 5496523 A (A. GAZIT ET AL.), 5 March 1996 (05.03.96), figures 5-7, abstract	1,2,9-11
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 February 1998	24-02-1998
Name and mailing address of the ISA/ Swedish Patent Office, Box 5055, S-102 42 STOCKHOLM	Authorized officer: Håkan Sandh

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 97/00603

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4461328 A (J.W. KENNEY), 24 July 1984 (24.07.84), claim 7, abstract --	1,2,9,10
X	US 4999164 A (H. PUCHINGER ET AL.), 12 March 1991 (12.03.91), column 1, line 64 - column 2, line 28, figures 1-4,9, abstract --	1,2,9,10
Y	WO 9411710 A1 (FLUILOGIC SYSTEMS OY ET AL.), 26 May 1994 (26.05.94), figures 1,10, claims 1-20, abstract --	1-14
PX	US 5580529 A (D.H. DEVAUGHN ET AL.), 3 December 1996 (03.12.96), figure 3, abstract -- --------	1,2,9-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

International application No.
PCT/FI 97/00603

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5364495 A	15/11/94	EP 0599394 A,B	01/06/94
		JP 6208031 A	26/07/94
		NL 9301071 A	16/01/95
US 5156811 A	20/10/92	NONE	
US 5496523 A	05/03/96	AU 2434295 A	29/11/95
		WO 9530483 A	16/11/95
US 4461328 A	24/07/84	NONE	
US 4999164 A	12/03/91	DE 3635598 A,C	05/05/88
		DE 3777064 A	09/04/92
		EP 0264704 A,B	27/04/88
		JP 63185457 A	01/08/88
WO 9411710 A1	26/05/94	CN 1097062 A	04/01/95
		EP 0620913 A	26/10/94
		FI 94675 B,C	30/06/95
		FI 925025 A	07/05/94
		JP 7506534 T	20/07/95
		US 5638986 A	17/06/97
US 5580529 A	03/12/96	CA 2147560 A	23/10/95